

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 June 2000 (02.06.00)	
International application No. PCT/US99/23685	Applicant's or agent's file reference 1159 WO
International filing date (day/month/year) 12 October 1999 (12.10.99)	Priority date (day/month/year) 12 October 1998 (12.10.98)
Applicant CANTRELL, Gary, L.	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

09 May 2000 (09.05.00)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Kiwa Mpay Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: LAWRENCE L. LIMPUS  
MALLINCKRODT INC.  
675 MCDONNELL BOULEVARD  
P.O. BOX 5840  
ST. LOUIS MO 63134

## FILE COPY 408

### WRITTEN OPINION

(PCT Rule 66)

Form PCT/IPEA/408 (cover sheet) (July 1998) DO NOT MAIL

Date of Mailing (day/month/year)		
Applicant's or agent's file reference  1159 WO		REPLY DUE within TWO months from the above date of mailing
International application No.  PCT/US99/23685	International filing date (day/month/year)  12 OCTOBER 1999	Priority date (day/month/year)  12 OCTOBER 1998
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 49/04, 9/50 and US Cl.: 424/9.52, 9.51, 502; 600/441, 458		
Applicant  MALLINCKRODT INC.		

<p>1. This written opinion is the <u>first</u> (first, etc.) drawn by this International Preliminary Examining Authority.</p> <p>2. This opinion contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the opinion</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step or industrial applicability</li> <li>IV <input checked="" type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input type="checkbox"/> Certain observations on the international application</li> </ul> <p>3. The applicant is hereby invited to reply to this opinion.</p> <p>When? See the time limit indicated above. <del>The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).</del></p> <p>How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.</p> <p>Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 <i>bis</i>. For an informal communication with the examiner, see Rule 66.6.</p> <p>If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.</p> <p>4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: <u>12 FEBRUARY 2001</u></p>	
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Facsimile No.  (703) 305-3230	Authorized officer AND Telephone No.  Michael G. Hartley (703) 308-1235
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I. Basis of the opinion

1. With regard to the elements of the international application:\*

the international application as originally filed

the description:

pages 1-39 , as originally filed

pages NONE , filed with the demand

pages NONE , filed with the letter of \_\_\_\_\_

the claims:

pages 40-43 , as originally filed

pages NONE , as amended (together with any statement) under Article 19

pages NONE , filed with the demand

pages NONE , filed with the letter of \_\_\_\_\_

the drawing:

pages 1-3 , as originally filed

pages NONE , filed with the demand

pages NONE , filed with the letter of \_\_\_\_\_

the sequence listing part of the description:

pages NONE , as originally filed

pages NONE , filed with the demand

pages NONE , filed with the letter of \_\_\_\_\_

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

the language of publication of the international application (under Rule 48.3(b)).

the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

contained in the international application in printed form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4.  The amendments have resulted in the cancellation of:

the description, pages NONE

the claims, Nos. NONE

the drawings, sheets/fig NONE

5.  This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

**II. Priority**

1.  This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
  - copy of the earlier application whose priority has been claimed.
  - translation of the earlier application whose priority has been claimed.
2.  This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

- the entire international application.
- claims Nos. \_\_

because:

- the said international application, or the said claim Nos. \_\_ relate to the following subject matter which does not require international preliminary examination (*specify*).

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_ are so unclear that no meaningful opinion could be formed (*specify*).

- the claims, or said claims Nos. \_\_ are so inadequately supported by the description that no meaningful opinion could be formed.

- no international search report has been established for said claims Nos. \_\_

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

**IV. Lack of unity of invention**

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees the applicant has:

- restricted the claims.
- paid additional fees.
- paid additional fees under protest.
- neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1 not to invite the applicant to restrict or pay additional fees:

Please See Supplemental Sheet.

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

- all parts.
- the parts relating to claims Nos. .

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. statement

Novelty (N)	Claims <u>1-20</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-20</u>	NO
Industrial Applicability (IA)	Claims <u>1-20</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over either one of Unger et al or Klaveness et al.

Unger disclose a composition useful as an ultrasound contrast agent comprising microbubbles encapsulating a gas within a shell, see abstract. The shells of the microbubbles (e.g., liposomes) may comprise bipolar compounds having intermolecular regions of mixed carbon chain length. For example, Unger discloses that the shell material may include fatty acids of up to 22 carbon atoms and that the lipids may be bound to a polymer, such as, polyethylene glycol, see columns 20-22. The polymers may be linked to the fatty acids via ester, amide, ether groups, etc., see column 22, lines 20-39. The shell materials taught by Unger et al. encompass those instantly claimed. Unger et al. teaches that the microbubbles may be made with a combination of shell materials, which would encompass the blend of bipolar compounds of the instantly claimed shell. Unger et al. teach methods of ultrasound imaging comprising administering said contrast agents, see column 29, line 47+.

Klaveness discloses a composition useful as an ultrasound contrast agent comprising microbubbles encapsulating a gas within an amphiphilic shell, see column 3, lines 9+. The shells of the microbubbles may comprise various bipolar compounds having intermolecular regions of mixed carbon chain length, such as, the mixed amphiphilic polymers as shown by formula I, column 4, as well as, the amphiphiles encompassed by formula II, column 5. These shell materials encompass those instantly claimed. The shells may include a blend of one or more of the amphiphilic materials, see column 2, lines 6+.

Although Unger et al. and Klaveness et al. do not specifically disclose that the shells of the microbubbles are made of a blend of bipolar compounds, it would have been obvious to one of ordinary skill in the art to use a blend of bipolar compounds, such as, those encompassed by the instant claims, because both Unger et al. and Klaveness et al. teach that a combination of shell materials may be employed to impart stability to the gas microbubbles, wherein many of the shell materials are within the scope of those encompassed by the instant claims. One of ordinary skill in the art would have been (Continued on Supplemental Sheet.)

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication Date ( <i>day/month/year</i> )	Filing Date ( <i>day/month/year</i> )	Priority date (valid claim) ( <i>day/month/year</i> )
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2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure ( <i>day/month/year</i> )	Date of written disclosure referring to non-written disclosure ( <i>day/month/year</i> )
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**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

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**TIME LIMIT:**

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

**IV. LACK OF UNITY OF INVENTION:**

2. Although this IPEA did not invite applicant to restrict or pay additional fees, Unity of Invention is lacking for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-13, drawn to a composition for ultrasound imaging comprising microbubbles comprising a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon chain length, as well as, a method of ultrasound imaging comprising administering said composition and taking an ultrasound image.

Group II, claim(s) 14-20, drawn to a method of measuring pressure or fluid flow rates comprising inserting a composition comprising microbubbles comprising a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon chain length into a closed system, measuring the acoustical changes with frequency  $f$  or the system and calculating the change in pressure or change in fluid flow rate.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature for the Group I invention is a pharmaceutical composition for *in vivo* ultrasound imaging and an *in vivo* diagnostic method of ultrasound imaging comprising administering said composition, while the special technical feature of the Group II invention is a method of measuring pressure of fluid flow rates by measuring the acoustic changes with frequency of a closed system and calculating the changes in pressure or change in flow rate.

**V. 2. REASoNED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

motivated to employ any of the shell materials in the microbubbles taught by Unger et al. or Klaveness et al. because Unger et al. and Klaveness et al. teach that various shell materials, including bipolar compounds, may be used as equivalents, in combinations with others, to impart stability to the shell of the microbubble.

Claims 14-20 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Tickner.

Unger et al. and Klaveness et al. fail to disclose the use of the ultrasound contrast agents for a method of measuring pressure or flow rates in a closed system, such as the circulatory system.

Tickner teaches a composition useful as a ultrasound contrast agent comprising microbubbles encapsulating a gas within a shell material. These microbubbles are analogous to those disclosed by Unger et al. and Klaveness et al. Tickner

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

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teaches that the microbubbles may further be used for methods of measuring the pressure within a closed system, such as, the cardiovascular system of a living being, see column 1. Tickner also teaches that the contrast agents may also be used to measure flow rate, see column 2, lines 18. Tickner teaches that these methods provide advantages in obtaining desired data, such as, blood pressure, see column 1, lines 27+.

It would have been obvious to one of ordinary skill in the art to use the contrast agents taught by Unger et al. or Klaveness et al. to measure pressure and/or flow rate because Tickner teaches that analogous and equivalent ultrasound contrast agent are also useful in such methods. One of ordinary skill in the art would have been motivated to employ the microbubbles disclosed by Unger et al. or Klaveness et al. in methods of measuring pressure or flow rate because Klaveness teaches that microbubbles are useful for such methods to provide a variety of desired data, including specific blood pressures in the cardiovascular system and blood pressure of patients in which the use of standard methods (e.g., a cuff) are not possible.

Claims 1-20 meet the criteria set out in PCT Article 33(2), because the prior art does not specifically teach the compositions having a blend of bipolar compounds and the methods of imaging, measuring pressure and/or flow rate using said compositions.

Claims 1-20 meet the criteria set out in PCT Article 33(4), because the instant claimed compositions and methods are useful as contrast agents for ultrasound imaging, as well as, for measuring pressure or flow rate of the circulatory system of a body.

----- NEW CITATIONS -----

NONE

## PATENT COOPERATION TREATY

PCT

REC'D 15 JAN 2001

WIPO

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1159 WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/23685	International filing date (day/month/year) 12 OCTOBER 1999	Priority date (day/month/year) 12 OCTOBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 49/04, 9/50 and US Cl.: 424/9.52, 9.51, 502; 600/441, 458		
Applicant MALLINCKRODT INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 09 MAY 2000	Date of completion of this report 20 NOVEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Michael G. Hartley Telephone No. (703) 308-1235
Facsimile No. (703) 305-3230	JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX <i>Joyce Bridgers for</i>

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23685

## I. Basis of the report

## 1. With regard to the elements of the international application:\*

 the international application as originally filed the description:pages 1-39, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_ the claims:pages 40-43, as originally filed  
pages NONE, as amended (together with any statement) under Article 19  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_ the drawings:pages 1-3, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_ the sequence listing part of the description:pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_

## 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

 the language of a translation furnished for the purposes of international search (under Rule 23.1(b)). the language of publication of the international application (under Rule 48.3(b)). the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

## 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

 contained in the international application in printed form. filed together with the international application in computer readable form. furnished subsequently to this Authority in written form. furnished subsequently to this Authority in computer readable form. The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished. The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4.  The amendments have resulted in the cancellation of: the description, pages NONE the claims, Nos. NONE the drawings, sheets/fig NONE5.  This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23685

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
  - restricted the claims.
  - paid additional fees.
  - paid additional fees under protest.
  - neither restricted nor paid additional fees.
2.  This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- complied with.
- not complied with for the following reasons:

Please See Supplemental Sheet.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
  - all parts.
  - the parts relating to claims Nos. ..

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23685

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims <u>1-20</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-20</u>	NO
Industrial Applicability (IA)	Claims <u>1-20</u>	YES
	Claims <u>NONE</u>	NO

**2. citations and explanations (Rule 70.7)**

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over either one of Unger et al or Klaveness et al.

Unger disclose a composition useful as an ultrasound contrast agent comprising microbubbles encapsulating a gas within a shell, see abstract. The shells of the microbubbles (e.g., liposomes) may comprise bipolar compounds having intermolecular regions of mixed carbon chain length. For example, Unger discloses that the shell material may include fatty acids of up to 22 carbon atoms and that the lipids may be bound to a polymer, such as, polyethylene glycol, see columns 20-22. The polymers may be linked to the fatty acids via ester, amide, ether groups, etc., see column 22, lines 20-39. The shell materials taught by Unger et al. encompass those instantly claimed. Unger et al. teaches that the microbubbles may be made with a combination of shell materials, which would encompass the blend of bipolar compounds of the instantly claimed shell. Unger et al. teach methods of ultrasound imaging comprising administering said contrast agents, see column 29, line 47+.

Klaveness discloses a composition useful as an ultrasound contrast agent comprising microbubbles encapsulating a gas within an amphiphilic shell, see column 3, lines 9+. The shells of the microbubbles may comprise various bipolar compounds having intermolecular regions of mixed carbon chain length, such as, the mixed amphiphilic polymers as shown by formula I, column 4, as well as, the amphiphiles encompassed by formula II, column 5. These shell materials encompass those instantly claimed. The shells may include a blend of one or more of the amphiphilic materials, see column 2, lines 6+.

Although Unger et al. and Klaveness et al. do not specifically disclose that the shells of the microbubbles are made of a blend of bipolar compounds, it would have been obvious to one of ordinary skill in the art to use a blend of bipolar compounds, such as, those encompassed by the instant claims, because both Unger et al. and Klaveness et al. teach that a combination of shell materials may be employed to impart stability to the gas microbubbles, wherein many of the shell materials are within the scope of those encompassed by the instant claims. One of ordinary skill in the art would have been (Continued on Supplemental Sheet.)

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

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**IV. LACK OF UNITY OF INVENTION:**

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2, and 13.3 is not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-13, drawn to a composition for ultrasound imaging comprising microbubbles comprising a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon chain length, as well as, a method of ultrasound imaging comprising administering said composition and taking an ultrasound image.

Group II, claim(s) 14-20, drawn to a method of measuring pressure or fluid flow rates comprising inserting a composition comprising microbubbles comprising a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon chain length into a closed system, measuring the acoustical changes with frequency for the system and calculating the change in pressure or change in fluid flow rate.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature for the Group I invention is a pharmaceutical composition for *in vivo* ultrasound imaging and an *in vivo* diagnostic method of ultrasound imaging comprising administering said composition, while the special technical feature of the Group II invention is a method of measuring pressure of fluid flow rates by measuring the acoustic changes with frequency of a closed system and calculating the changes in pressure or change in flow rate.

**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

motivated to employ any of the shell materials in the microbubbles taught by Unger et al. or Klaveness et al. because Unger et al. and Klaveness et al. teach that various shell materials, including bipolar compounds, may be used as equivalents, in combinations with others, to impart stability to the shell of the microbubble.

Claims 14-20 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Tickner.

Unger et al. and Klaveness et al. fail to disclose the use of the ultrasound contrast agents for a method of measuring pressure or flow rates in a closed system, such as the circulatory system.

Tickner teaches a composition useful as a ultrasound contrast agent comprising microbubbles encapsulating a gas within a shell material. These microbubbles are analogous to those disclosed by Unger et al. and Klaveness et al. Ticker teaches that the microbubbles may further be used for methods of measuring the pressure within a closed system, such as, the cardiovascular system of a living being, see column 1. Tickner also teaches that the contrast agents may also be used to measure flow rate, see column 2, lines 18. Tickner teaches that these methods provide advantages in obtaining desired data, such as, blood pressure, see column 1, lines 27+.

It would have been obvious to one of ordinary skill in the art to use the contrast agents taught by Unger et al. or Klaveness et al. to measure pressure and/or flow rate because Tickner teaches that analogous and equivalent ultrasound contrast agent are also useful in such methods. One of ordinary skill in the art would have been motivated to employ the microbubbles disclosed by Unger et al. or Klaveness et al. in methods of measuring pressure or flow rate because Klaveness teaches that microbubbles are useful for such methods to provide a variety of desired data, including specific blood pressures in the cardiovascular system and blood pressure of patients in which the use of standard methods (e.g., a cuff) are not possible.

Claims 1-20 meet the criteria set out in PCT Article 33(2), because the prior art does not specifically teach the compositions having a blend of bipolar compounds and the methods of imaging, measuring pressure and/or flow rate using said

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/23685

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

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compositions.

Claims 1-20 meet the criteria set out in PCT Article 33(4), because the instant claimed compositions and methods are useful as contrast agents for ultrasound imaging, as well as, for measuring pressure or flow rate of the circulatory system of a body.

----- NEW CITATIONS -----

NONE

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/23685

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 49/04, 9/50  
 US CL :424/9.52, 9.51, 502; 600/441, 458  
 According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9.52, 9.51, 502, 489, 498, 450; 600/441, 458

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,585,112 A (UNGER et al.) 17 December 1996, see abstract and columns 20-22, especially column 22, lines 6-39.	1-20
Y	US 5,536,490 A (KLAVENESS et al.) 16 July 1996, see abstract and columns 4-8.	1-20
Y	US 4,684,479 A (D'ARRIGO) 04 August 1987, see columns 2-3.	1-20
Y	US 4,265,251 A (TICKNER) 01 May 1981, see column 2, lines 7-20.	14-20

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention is not be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 JANUARY 2000

Date of mailing of the international search report

07 FEB 2000

Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

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Authorized officer

Michael G. Hartley

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**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US99/23685

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**  

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US99/23685

**B. FIELDS SEARCHED**

Electronic data bases consulted (Name of data base and where practicable terms used):

**EAST (APS)**

search terms: ultrasound, imaging, microbubbles, docosanoate, octacosanoate, docosamide, PEG, fatty acids, pressure, acoustic, flow rate

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING**

This ISA for 1 multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-13, drawn to a composition for ultrasound imaging comprising microbubbles comprising a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon chain length, as well as, a method of ultrasound imaging comprising administering said composition and taking an ultrasound image.

Group II, claim(s) 14-20, drawn to a method of measuring pressure or fluid flow rates comprising inserting a composition comprising microbubbles comprising a gas within a shell made from a blend of bipolar compounds having intermolecular hydrophobic regions of mixed carbon chain length into a closed system, measuring the acoustical changes with frequency for the system and calculating the change in pressure or change in fluid flow rate.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature for the Group I invention is a pharmaceutical composition for *in vivo* ultrasound imaging and an *in vivo* diagnostic method of ultrasound imaging comprising administering said composition, while the special technical feature of the Group II invention is a method of measuring pressure or fluid flow rates by measuring the acoustic changes with frequency of a closed system and calculating the changes in pressure or change in flow rate.